PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/534358

Applicant's or agent's file reference FPP3019	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/04998	International filing date *(day/month/year)* 03.11.2003	Priority date *(day/month/year)* 07.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C211/42		
Applicant NADKARNI, Sunil Sadanand		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	07.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/04998

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-21 received on 21.10.2004 with letter of 18.10.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V ----------

(The numbering of the prior art documents (D1,D2..) cited hereinafter corresponds to the order in which they are mentioned in the International Search Report.)

Polymorphic Form V of sertraline hydrochloride has already been known in the art, see e.g. D3. In view of D3, which may be considered as closest prior art, the technical problem to be solved by the present invention can be seen in the provision of a simple, more efficient and cost-effective process for producing the target compound.

The present process as claimed in claim 1 is essentially characterized by dissolving or suspending **sertraline mandelate** in a **protic solvent** (mixture), reducing the pH of the solution or suspension by adding **hydrochloric acid** in water to form a clear solution and isolating sertraline hydrochloric Form V therefrom.

The present process differs from the process as described in D3 (see pages 6-10) at least with respect to the starting material (D3: **sertraline hydrochloride** or **sertraline base** which are obtained from sertraline mandelate in (an) additional process step(s)). There is no teaching or suggestion to be found in D3 to start the preparation of Form V directly from sertraline mandelate.
D2 describes the preparation of semi-stable polymorphic **Form II** of sertraline hydrochloride by using **aprotic** solvents.
D4 teaches the preparation of an inorganic salt of an optically active phenylglycine derivative via an asymmetric transformation followed by a treatment of the reaction mixture obtained with a strong inorganic acid. No particular relevance of this teaching with respect to the present invention is apparent.
The subject-matter of present claims 1-13,21 is thus considered to meet the requirements of Art. 33(2)-(4) PCT.

Claims 14-20 relate to a process for the preparation of an **immediate release** pharmaceutical composition using sertraline hydrochloride Form V having the indicated properties (particle size, impurity level etc.) which have been found to give optimal results. The available prior art (closest D3, page 17, and/or D5, in particular, page 22, line 9 - page 25, line 16 and Examples 6A,6B, describing compositions for controlled release) is silent about the optimal characteristics of sertraline hydrochloride **Form V** in pharmaceutical applications. The subject-matter of claims 14-20 may thus also considered to meet the criteria of Art. 33(2)-(4) PCT.

CLAIMS

1. A process for the production of sertraline hydrochloride Form-V comprising the steps of:

   a) dissolving or suspending sertraline mandelate in a protic solvent or a mixture of protic solvents;

   b) reducing the pH of the solution or the suspension by adding hydrochloric acid in water to form a clear solution; and

   c) isolating sertraline hydrochloride Form V.

2. The process as claimed in claim 1, wherein protic solvent(s) used in step (a) is selected from the group comprising of alcohol , water or mixtures thereof.

3. The process as claimed in claim 2, wherein said alcoholic solvent used in step (a) is selected from the group comprising of methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, t-butyl alcohol and isobutyl alcohol or a mixture thereof.

4. The process as claimed in claim 3, wherein said alcoholic solvent is isopropyl alcohol.

5. The process as claimed in claim 1, wherein said step(a) of dissolving or suspending is achieved by heating and / or stirring.

6. The process as claimed in claim 1, wherein said step (a) of dissolving or suspending sertraline mandelate in a solvent is carried out at temperature in the range of 20 to 90 °C.

7. The process as claimed in claim 6, wherein said range of temperature is 25 to 80°C.

8. The process as claimed in claim 7, wherein said range of temperature is 25 to 30°C.

9. The process as claimed in claim 1, wherein pH is reduced to the range of 1 to 3 in step (b).

10. The process as claimed in claim 9, wherein pH is reduced to the range of 1 to 2.

11. The process as claimed in claim 1, wherein isolation of sertraline hydrochloride Form V in step (c) is carried out by cooling the contents of step (b).

12. The process as claimed in claim 11, wherein the cooling is effected by allowing the solution to attain room temperature on its own or with mild coolants comprising of cold water, water, alcohol or mixtures thereof.

13. The process as claimed in claim 12, wherein said alcohol is selected from the group comprising of monohydroxy alcohols, dihydroxy alcohols or mixtures thereof.

14. A process for preparation of an immediate release pharmaceutical composition of sertraline hydrochloride Form - V, comprising mixing sertraline hydrochloride Form-V, of particle size below 20μ is not less than 90 % with pharmaceutically acceptable diluent, carrier or excepient.

15. The process for preparation of a pharmaceutical composition as claimed in claim 14, wherein the impurity level in sertraline hydrochloride Form V used is not more than 0.50% comprising of both known and unknown impurities.

16. The process for preparation of a pharmaceutical composition as claimed in claim 15, wherein the sulphated ash in sertraline hydrochloride Form V is not more than 0.2%.

17. The process for preparation of a pharmaceutical composition as claimed in claim 15, wherein the heavy metals in sertraline hydrochloride Form V used is not more than 20 ppm.

18. The process for preparation of a pharmaceutical composition as claimed in claim 14, wherein the assay by titration of sertraline hydrochloride Form V is between 98.0 to 102.0 % on anhydrous basis.

19. The process for preparation of a pharmaceutical composition of as claimed in claim 14, wherein the residual solvents in the active ingredient sertraline hydrochloride Form V are :

(a) isopropyl alcohol	:	not more than 2000 ppm
(b) methanol	:	not more than 100 ppm
(c) acetone	:	not more than 100 ppm
(d) methylene chloride	:	not more than 200 ppm

20. The process for preparation of a pharmaceutical composition as claimed in claim 14, wherein the microbial limits in active ingredient sertraline hydrochloride Form V are :

total aerobic count (cfu/g)	:	not more than 1000
total fungal count (cfu/g)	:	not more than 100
E.Coli	:	should be absent.

21. A process for the preparation of sertraline hydrochloride Form - V, substantially as herein described, particularly with reference to the foregoing examples.